Prevalence and risk factors associated with perianal ulcer in advanced acquired immunodeficiency syndrome

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Background: The aims of this study were to evaluate the prevalence of perianal ulcer in AIDS patients with advanced disease, and to investigate risk factors associated with these lesions.

Methods: A cross-sectional study was conducted to determine the prevalence and risk factors associated with the presence of perianal ulcer in AIDS patients. A type-specific polymerase chain reaction (PCR) assay was carried out for detection of herpes simplex virus (HSV) DNA on swabs obtained from the ulcerative lesions.

Results: In total, 272 hospitalized AIDS patients were included in the study, for evaluation of the risk factors associated with the lesion. Perianal ulceration was found in 25 of 272 patients (prevalence=9.2%). The presence of HSV DNA was shown by type-specific PCR in 22 of 23 (95.6%) patients. Multivariate analysis revealed that a history of esophageal candidiasis (odds ratio (OR)=15.1; 95% confidence interval (CI)=3.8–59.1) and a history of perianal ulcer (OR=19.2; 95% CI 6.4–58.1) were significant risk factors for the presence of perianal ulcer.

Conclusion: We conclude that a history of perianal ulcer and a history of esophageal candidiasis were risk factors independently associated with perianal ulcer in AIDS patients with advanced disease.

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INTRODUCTION

Ulcerated perianal lesions are commonly observed in patients with AIDS. In advanced stages of disease, prevalence rates as high as 10–14% have been reported.[1–4] Unless a specific treatment is implemented, these lesions may continue to enlarge peripherally, causing pain and discomfort, and may increase in size up to 100 cm^2.[5–8]

Mucocutaneous ulcers caused by herpes simplex virus (HSV) are usually diagnosed by viral culture from a swab sample obtained from the lesion.[9,10] The polymerase chain reaction (PCR) has been used to detect genital ulcers and also asymptomatic anogenital shedding of HSV.[11,12] PCR was recently shown to be useful in detecting HSV DNA in perianal ulcers of AIDS patients.[4] However, although HSV seems to be the main etiologic agent, cytomegalovirus, *Treponema pallidum* and other agents have also been associated with perianal ulceration.[1,13–16]

While perianal ulceration is a common cause of morbidity in AIDS patients, data on risk factors for this condition are scarce. The aim of this study was to determine the prevalence and risk factors for perianal ulcer in patients with advanced AIDS.

PATIENTS AND METHODS

Setting

The Instituto de Infectologia Emílio Ribas (IIER), São Paulo City, Brazil, is a 250-bed, tertiary-care, state hospital for infectious diseases. In recent years, half of its beds have been occupied by AIDS patients.

Patients and study design

A cross-sectional study was conducted to estimate the prevalence and to evaluate risk factors that might predict perianal ulcer in AIDS patients. Over an 8-month period (October 1996 to June 1997), all class C AIDS patients (classified according to modified CDC criteria),[17] aged at least 18 years old, who were consecutively admitted to the IIER, were examined for the presence of perianal ulcer. Each patient was seen within 72 h of admission. If a patient was hospitalized more than once, only the first hospitalization was considered.

The patients were given a standardized, structured questionnaire. One hundred and forty-five patients who could not answer the questionnaire because of cognitive

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disorders or a severe clinical condition were considered ineligible. Twenty-nine other cases had been hospitalized for the investigation of signs or symptoms associated with HIV infection, but could not be classified as AIDS cases and were not included in the study.

Before being interviewed, 38 patients died, 30 were discharged from the hospital, and 16 had been hospitalized twice. Thus, in total, 288 patients were eligible for the study. Of these, 16 refused to participate, and 272 were included. All investigations were performed after informed consent was obtained. This study was approved by the Committee of Ethical Research of the IIER.

Data and specimen collection

The patients were interviewed privately in the hospital by one of the authors, using a questionnaire that addressed indicators of socioeconomic status (per capita income and educational level) and sexual activity. Variables related to previous or present opportunistic diseases and risk behavior for HIV infection were also investigated. The per capita income was obtained by dividing the number of minimum wages received per residence by the number of subjects living in the same dwelling. Educational level was classified as none, elementary (complete or incomplete), secondary (complete or incomplete), and college (university, complete or incomplete).

Receptive anal intercourse, history of genital ulcer and history of perianal ulcer were investigated through personal history and hospital records.

The occurrence of opportunistic infectious diseases was investigated by consulting hospital records and the physician assigned to each patient.

The perianal region of all study participants was examined by the same investigator. Perianal ulcer was defined by the presence of an ulcerative lesion detected by medical examination. When a perianal ulcer was detected, a pre-moistened cotton-tipped swab was rubbed over the perianal ulcer, and the specimen was placed in 3 mL of Hanks balanced salt solution containing antibiotics (vancomycin and amphotericin B). Samples were taken to the laboratory within 2 h of collection.

Detection of HSV DNA by PCR

A type-specific, PCR-based assay was used for detection and direct typing, as described previously.[4] This assay exploits differences between the DNA sequences of the DNA polymerase genes of HSV-1 and HSV-2.

Statistical analysis

To estimate the association between perianal ulcer and the variables of interest, odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression.[18] Statistical significance was evaluated by the likelihood ratio (LR) test. For factors susceptible to ranking, a test for linear trend was used.

Logistic regression was used to construct a model to control for the potential confounding effects of other variables. Age and the factors found to be significantly related to perianal ulcer in univariate analysis were included in the final model. Variables with more than 20% missing values were not included in the final model.

RESULTS

Perianal ulcer was found in 25 of the 272 patients studied (prevalence=9.2%; 95% CI 6.0–13.3%).

A perianal swab was obtained from 23 of the 25 subjects with perianal ulcer. Of the two patients from whom a perianal swab was not obtained, one did not allow specimen collection, and the other had used acyclovir for more than 1 month to treat a recurrent lesion. Overall, HSV DNA was detected in 22 of 23 (95.7%) cases by PCR. This type-specific assay detected HSV type 2 in all samples.

No differences were observed in the demographic characteristics of AIDS patients with and without perianal ulcer (Table 1).

Regarding risk behavior for HIV infection, men reporting male–male sex showed the highest risk of perianal ulcer (OR=4.1; 95% CI 1.3–12.8) (Table 2). Seventy-five patients (27.6%) reported drug addiction, and five (1.8%) reported HIV infection through blood transfusion. None of these variables was associated with perianal ulcer. The lesion was more frequent among patients reporting receptive anal intercourse (OR=3.0; 95% CI 1.3–7.0). A history of genital ulcer was reported by 13.2% of patients with perianal ulcer (OR=1.8; 95% CI 0.7–4.5). Among the variables related to sexual behavior, history of perianal ulcer was the strongest predictor for perianal ulcer (OR=9.9; 95% CI 4.1–24.1) (Table 2).

Overall, pulmonary tuberculosis was the most prevalent opportunistic infection among the 272 AIDS patients studied, being observed in 128 of 270 (47.4%) subjects. However, esophageal candidiasis was the only opportunistic infection significantly associated with perianal ulcer (OR=6.7; 95% CI 2.2–20.2) (Table 3).

The effect of antiretroviral agents was considered only for those patients undergoing treatment for 2 months prior to entering the study. In total, 141 (54.2%) patients were receiving highly active antiretroviral therapy (HAART); the prevalence of perianal ulcer (9.9%) was similar to that found among patients not receiving this therapy (9.2%) (Table 4).

The $CD4^+$ cell counts considered were those obtained within 3 months of the interview. The median $CD4^+$ cell count of the patients in the present study was 25 cells/mm^3. The association between the prevalence of perianal ulcer and $CD4^+$ cell counts was nearly significant (P=0.054) (Table 4).

Table 1. Prevalence of perianal ulcer in AIDS patients according to sociodemographic characteristics and associated odds ratios (OR)

Characteristics	*Total*	*Perianal ulcer*		*OR*	*95% CI*
		No.	*%*		
Age (years)					
≤30[a]	91	8	8.8	1.0	–
31–40	122	9	7.4	0.8	0.3–2.2
>40	59	8	13.6	1.6	0.6–4.6
LR (1 df)=0.70; P=0.40					
Sex					
Female[a]	69	6	8.7	1.0	–
Male	203	19	9.4	1.1	0.4–2.8
LR (1 df)=0.03; P=0.87					
Family per capita income (minimal wages)[b]					
≤0.5[a]	47	2	4.3	1.0	–
0.6–3.0	88	8	9.1	2.3	0.5–11.1
>3.0	64	8	12.5	3.2	0.7–15.9
LR (1 df)=2.6; P=0.11					
Educational level[c]					
None[a]	19	1	5.3	1.0	–
Primary	162	14	8.6	1.7	0.2–13.7
Secondary	60	6	10.0	2.0	0.2–17.8
College	30	4	13.3	2.8	0.3–26.9
LR (1 df)=0.97; P=0.33					

[a]Reference group. [b]Data not available for 73 patients. [c]Data not available for one patient.

Univariate analysis showed that the factors associated with perianal ulcer were: male–male sex (OR =4.1; 95% CI 1.3–12.8), history of perianal ulcer (OR=9.9; 95% CI 4.1–24.1), history of esophageal candidiasis (OR=6.7; 95% CI 2.2–20.2), and history of receptive anal intercourse (OR=3.0; 95% CI 1.3–7.0). Age and all of these factors, except male–male sex (not applicable to female patients), were included in the final model (Table 5). The variables shown to be risk factors for perianal ulcer at a statistically significant level were history of esophageal candidiasis (OR=15.1; 95% CI 3.8–59.1) and history of perianal ulcer (OR=19.2; 95% CI 6.4–58.1).

Table 2. Prevalence of perianal ulcer in AIDS patients according to some risk factors for HIV infection and some sexual activity indicators, and associated odds ratios (OR)

Characteristics	*Total*	*Perianal ulcer*		*OR*	*95% CI*
		No.	*%*		
Male–male sex					
No[a]	100	4	4.0	1.0	–
Yes	103	15	14.6	4.1	1.3–12.8
LR (1 df)=7.1; P=0.01					
Lifetime number of sexual partners[b]					
<5[a]	58	4	6.9	1.0	–
6–10	40	5	12.5	1.9	0.5–7.7
>10	98	7	7.1	1.0	0.3–3.7
LR (1 df)=0.01; P=0.94					
History of perianal ulcer[c]					
No[a]	231	12	5.2	1.0	–
Yes	37	13	35.1	9.9	4.1–24.1
LR (1 df)=23.88; P<0.001					
History of genital ulcer[d]					
No[a]	191	15	7.9	1.0	–
Yes	76	10	13.2	1.8	0.7–4.5
LR (1 df)=1.80; P=0.18					
Receptive anal intercourse[e]					
Never[a]	152	9	5.9	1.0	–
Ever	102	16	15.7	3.0	1.3–7.0
LR (1 df)=7.54; P=0.02					

[a]Reference group. [b]Data not available for 76 patients. [c]Data not available for 4 patients. [d]Data not available for 5 patients. [e]Data not available for 18 patients.

Table 3. Prevalence of perianal ulcer in AIDS patients according to opportunistic diseases and associated odds ratios (OR)

		Perianal ulcer			
Opportunistic disease	*Total*	*No.*	*%*	*OR*	*95% CI*
Pulmonary tuberculosis[a]					
No[b]	142	12	8.5	1.0	–
Yes	128	13	10.2	1.2	0.5–2.8
LR (1 df)=0.23; P=0.63					
Extrapulmonary tuberculosis[a]					
No[b]	226	20	8.9	1.0	–
Yes	44	5	11.4	1.3	0.5–3.7
LR (1 df)=0.26; P=0.61					
Mycobacteriosis[a]					
No[b]	253	21	8.3	1.0	–
Yes	17	4	23.5	3.4	1.0–11.4
LR (1 df)=3.30; P=0.07					
CNS cryptococcosis[a]					
No[b]	240	24	10.0	1.0	–
Yes	30	1	3.3	0.3	0.04–2.4
LR (1 df)=1.78; P=0.18					
Esophageal candidiasis[a]					
No[b]	253	19	7.5	1.0	–
Yes	17	6	35.3	6.7	2.2–20.2
LR (1 df)=9.60; P=0.002					
CNS toxoplasmosis[a]					
No[b]	193	17	8.8	1.0	–
Yes	77	8	10.4	1.2	0.5–2.9
LR (1 df)=0.16; P=0.69					
Pulmonary pneumocystosis[a]					
No[b]	187	18	9.6	1.0	–
Yes	83	7	8.4	0.9	0.3–2.2
LR (1 df)=0.10; P=0.75					
Cytomegalovirus disease[a]					
No[b]	234	22	9.4	1.0	–
Yes	36	3	8.3	0.9	0.2–3.1
LR (1 df)=0.04; P=0.84					
Kaposi's sarcoma[a]					
No[b]	255	22	8.6	1.0	–
Yes	15	3	20.0	2.6	0.7–10.1
LR (1 df)=1.72; P=0.19					

[a]Data not available for two patients.
[b]Reference group.
CNS, central nervous system.

Table 4. Prevalence of perianal ulcer in AIDS patients according to CD4+ cell count and use of HAART and associated odds ratios (OR)

		Perianal ulcer			
Characteristics	*Total*	*No.*	*%*	*OR*	*95% CI*
CD4+ cell count[a]					
≤50[b]	125	19	15.2	1.0	–
51–200	60	4	6.7	0.4	0.1–0.2
>200	32	2	6.3	0.4	0.1–1.7
LR (1 df)=3.72; P=0.054					
HAART[c]					
No[b]	119	11	9.2	1.0	–
Yes	141	14	9.9	1.1	0.5–2.5
LR (1 df)=0.04; P=0.85					

[a]Data not available for 55 patients.
[b]Reference group.
[c]Data not available for 12 patients.

Table 5. Crude and adjusted odds ratios (OR) of perianal ulcer in AIDS patients associated with selected factors

Characteristics	*Crude OR*	*OR*[a]	*95% CI*
Age (years)			
≤30	1.0	1.0	–
31–40	0.8	0.7	0.2–2.4
>40	1.6	3.8	1.0–13.4
LR (1 df)=3.19; P=0.07			
Esophageal candidiasis			
No	1.0	1.0	–
Yes	6.7	15.1	3.8–59.1
LR (1 df)=13.9; P<0.001			
History of perianal ulcer			
No	1.0	1.0	–
Yes	9.9	19.2	6.4–58.1
LR (1 df)=24.4; P<0.001			
Receptive anal intercourse			
No	1.0	1.0	–
Yes	3.0	1.8	0.7–5.0
LR (1 df)=1.4; P=0.2			

[a]Odds ratios adjusted for all the factors included in the table.

DISCUSSION

In the present study, the prevalence of perianal ulcer was 9.2% among 272 AIDS patients hospitalized for treatment of opportunistic infections. In most (95.5%), HSV DNA was detected in the lesion by PCR.

In a previous study, HSV DNA could be demonstrated in 36 of 41 (87.8%) perianal ulcers of AIDS patients using the same PCR assay,[4] and all of the five PCR-negative patients had other etiologies for the ulcer. In the present study, HSV DNA was not detected in only a single case (1/23); however, the ulcer healed 2 weeks after treatment with oral acyclovir. This finding highlights the role of HSV as the most important etiologic agent in perianal ulcers in patients with advanced AIDS.

The prevalence of HSV ulcerative lesions increases in AIDS patients with advanced immunodepression (measured by $CD4^+$ cell counts).[19] In the present study, the median $CD4^+$ cell count was lower in AIDS patients with perianal ulcer (25 cells/mm^3) than in patients without the lesion (76 cells/mm^3). However, only a marginal association was found between the presence of perianal ulcer and $CD4^+$ cell counts (P=0.054). All patients in the present study were hospitalized for the treatment or investigation of an opportunistic disease, and the majority had <50 $CD4^+$ cells/mm^3 (median 25 cells/mm^3). This fact may have led to homogeneity in $CD4^+$ cell counts within the group, and may be the underlying reason for the lack of association between perianal ulcer and $CD4^+$ cell count in this study.

A substantial decrease in the incidence of Kaposi's sarcoma, non-Hodgkin's lymphoma and opportunistic infections has been observed after the introduction of HAART.[20–23] In an era of widespread use of HAART, the fact that 119 (45.8%) patients were not receiving a potent combination of antiretroviral therapy may have led to an overestimation of the prevalence of perianal ulcer. Otherwise, the prevalence of perianal ulcer in the present series might have been even higher had patients who died or who could not be assessed because of cognitive disorders or severe clinical conditions been included in the present study.

The sociodemographic characteristics were not associated with the presence of ulcerative perianal lesions in this study.

Overall, the most prevalent opportunistic infection diagnosed in the present study was pulmonary tuberculosis, observed in 47.4% of patients. This finding was expected, considering the high prevalence of tuberculosis in Brazil, and that this incidence is higher when $CD4^+$ cell counts are less than 200 cells/mm^3.[24,25]

The only opportunistic disease that was an independent risk factor for perianal ulcer in AIDS patients was esophageal candidiasis (OR=15.1; 95% CI 3.8–59.1). Since there is no pathogenic relationship between these two entities, a possible explanation is that both esophageal candidiasis and herpetic perianal ulcer occur more frequently in highly immunocompromised patients. The low median $CD4^+$ cell counts of the patients in the present study (25 cells/mm^3) support this idea.

Based on controlled studies,[26,27] the 1999 US Public Health Service and Infectious Diseases Society of America guidelines for the prevention of opportunistic infections in persons infected with immunodeficiency virus recommend daily suppressive therapy when HSV recurrences are frequent or severe.[28] In the present study, the strong association between history of perianal ulcer and a subsequent lesion (OR=19.2; 95% CI 6.4–58.1) provides additional support for this recommendation.

Receptive anal intercourse was associated with perianal ulcer in the univariate analysis (P=0.02), but was not statistically significant when tested in the multivariate analysis. However, underestimation of the number of subjects declaring this practice may have led to some degree of misclassification. The variable male–male sex was also associated with the lesion in the univariate analysis (OR=4.1; 95% CI 1.3–12.8), but was not statistically significant in the regression model.

We conclude that the prevalence of perianal ulcer in AIDS patients hospitalized for treatment of other opportunistic infections is high, and that HSV-2 is responsible. A history of perianal ulcer and a history of esophageal candidiasis are strong risk factors independently associated with perianal ulcer in AIDS patients.

Controlled studies would be useful to establish the benefit of prophylaxis with acyclovir in this particular subset of AIDS patients.

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